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FOLEY & LARDNER LLP
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER	
JUNG, UNSU	

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/728,067	BUECHLER ET AL.	
	Examiner	Art Unit	
	Unsu Jung	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-36,40,41,43 and 44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-36,40,41,43 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 April 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/2/07 & 6/25/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's reply filed on April 2, 2007 have been acknowledged and entered. The reply filed on April 2, 2007 includes following amendments:

- Specification and Fig. 2 have been amended; and
- Claims 1-31, 37-39, and 42 have been canceled and claims 32-34, 40, 43, and 44 have been amended.

It has been noted that the status identifier for claim 43 incorrectly indicates as being "original." The status identifier for claim 43 should be "currently amended" as claim 43 has bee amended in the reply filed on April 2, 2007.

2. Claims 32-36, 40, 41, 43, and 44 are pending and under consideration for their merits.

Sequence Compliance

3. Although Applicant indicates that a sequence listing has been provided along with a computer readable disk and an appropriate certification in the reply filed on April 2, 2007 (p7), no such document was found. Therefore, the current Application remains non-compliant with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below.

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicants must file the items indicated below within the time period set forth in this Office Action to avoid abandonment under 35 U.S.C. 133 (extensions of time may be obtained under the provisions of 35 CFR 1.136(a)). The amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 35 CFR 1.821-1.825 for the following reasons(s):

- This application clearly fails to comply with the requirements of 37 CFR 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rule making notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- A paper copy of the "Sequence Listing" for sequences on p24 (SEQ ID NO:1 and SEQ ID NO:2) of the specification, as well as an amendment specifically directing its entry into the application has not been submitted.
- A copy of "Sequence Listing" for sequences on p24 (SEQ ID NO:1 and SEQ ID NO:2) of the specification in computer readable form has not been submitted as required by 37 CFR 1.821(e).

- A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, has not been submitted as required by 37 CFR 1.821(e) or 1.821(f) or 1.821 (g) or 1.825(b) or 1.825(d).

Applicants must provide:

- A paper copy of the "Sequence Listing", as well as an amendment specifically directing its entry into the application
- A copy of "Sequence Listing" in computer readable form as required by 37 CFR 1.821(e)
- A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821 (g) or 1.825(b) or 1.825(d)
- Sequence identifiers and sequence ID numbers for the sequences listed throughout the specification

Applicant is required to thoroughly review the specification and comply with all sequence rules. Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with 37 CFR 1.821(c), reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

If a complete response has not been submitted by the time the shortened statutory period for response set THREE MONTHS from the mailing date of this action has expired, this application will become abandoned unless applicant corrects the deficiency and obtains an extension of time under 37 C.F.R. 1.136. In no case may an applicant extend the period for response beyond the six month statutory period.

Objections Withdrawn

5. Applicant's arguments, see p8, filed on April 2, 2007, with respect to the objection of the drawings have been fully considered and are persuasive. The objection of the drawings has been withdrawn in view of the amended Fig. 2 in the reply filed on April 2, 2007.

6. Applicant's arguments, see p8, filed on April 2, 2007, with respect to the objection of the specification have been fully considered and are persuasive. The objection of the specification has been withdrawn in view of the amended specification in the reply filed on April 2, 2007.

Rejections Withdrawn

7. The rejection of claims 32, 34, 40, 41, 43, and 44 under 35 U.S.C. 112, second paragraph has been withdrawn in view of the amended claims 32, 34, 40, and 44 and canceled claims 37-39 and 42 in the reply filed on April 2, 2007.

Claim Rejections - 35 USC § 112, First Paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Written Description

Claims 40 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." MPEP § 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. The MPEP states that:

"The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction

to practice...or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus" MPEP § 2163.

The MPEP does state that for a generic claim, the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitutes a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosures of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli* 872, F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a method of identifying an increased risk of subclinical atherosclerosis in a human subject, comprising the steps of performing an assay that detects monocyte chemoattractant protein-1 (MCP-1) in a blood sample from the subject to provide a MCP-1 assay result and correlating the MCP-1 assay result to risk of the presence or absence of subclinical atherosclerosis in the subject. The invention is further drawn to assaying for additional subject-derived specific markers of myocardial injury, neural tissue injury, blood pressure regulation, coagulation, hemostasis, inflammation, and apoptosis.

The claims are not limited as to the number of markers, since claims 40 and 41 recite "determining the presence or amount of one or more subject-derived markers" and would encompass, for example 216 different subject-derived markers as disclosed in the current specification (pp58-62) as well as those markers not listed in the specification. Further, claim 41 is directed to assaying for additional subject-derived specific markers of myocardial injury, neural tissue injury, blood pressure regulation, coagulation, hemostasis, inflammation, and apoptosis and the currently recited claims would include list of markers disclosed in the current specification (216 markers, pp58-62) as well as those specific markers not listed in the specification.

It does not appear based upon the limited disclosure of additional subject-derived specific markers of myocardial injury, neural tissue injury, blood pressure regulation, coagulation, hemostasis, inflammation, and apoptosis alone that Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the limited number of species disclosed and the extensive variation permitted within the genus "subject-derived specific markers of myocardial injury, neural tissue injury, blood pressure regulation, coagulation, hemostasis, inflammation, and apoptosis."

Since each marker represents a unique polypeptide of distinct structure and functional properties, methods that involve the detection of different markers or different sets of markers would differ substantially. For example, any given marker would not be capable of identifying an increased risk of atherosclerosis. In light of substantial variance among the genus of methods claimed, one skilled in the art would not

understand the inventor(s) to have possession of the entire genus based on the limited methods described.

Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time of the application was filed, had possession of the entire genus of the claimed invention.

10. Enablement

Claims 32-36, 40, 41, 43, and 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention is drawn to a method of identifying an increased risk of atherosclerosis in a human subject, comprising the steps of performing an assay that detects MCP-1 in a blood sample from the subject to provide a MCP-1 assay result and correlating the MCP-1 assay result to risk of the presence or absence of subclinical atherosclerosis in the subject. The invention is further drawn to assaying for additional subject-derived specific markers of myocardial injury, neural tissue injury, blood pressure regulation, coagulation, hemostasis, inflammation, and apoptosis.

As disclosed in the current specification (p23, paragraph [0064]), MCP-1 has been implicated in the pathogenesis of a variety of diseases that involve monocyte

infiltration, including psoriasis, rheumatoid arthritis, and atherosclerosis. The normal concentration of MCP-1 in plasma is <0.1 ng/ml. The plasma concentration of MCP-1 is elevated in patients with acute myocardial infarction (AMI), and may be elevated in the plasma of patients with unstable angina, but no elevations have been associated with stable angina (Soejima et al., *J. Am. Coll. Cardiol.* 1999, Vol. 34, pp983-988; Nishiyama et al., *Jpn. Circ. J.*, 1998, Vol. 62, pp710-712; Matsumori et al., *J. Mol. Cell. Cardiol.*, 1997, Vol. 29, pp419-423). The current specification (p23, paragraph [0065]) further discloses that elevations of the serum concentration of MCP-1 are associated with various conditions associated with inflammation, including alcoholic liver disease, interstitial lung disease, sepsis, and systemic lupus erythematosus (Fisher et al., *Gut*, 1999, Vol. 45, pp416-420; Suga et al., *Eur. Respir. J.*, 1999, Vol. 14, pp376-382; Bossink et al., *Blood*, 1995, Vol. 86, pp3841-3847; Kaneko et al. *J. Rheumatol.*, 1999, Vol. 26, pp568-573). Further, MCP-1 is a specific marker of the presence of a pro-inflammatory condition that involves monocyte migration.

The current state of the art (Vasan, *Circulation*, 2006, Vol. 113, pp2335-2362) of cardiovascular disease teaches that biomarkers are used to identify high-risk individuals to diagnose disease conditions promptly and accurately (p2335). Vasan teaches that biomarkers can be used as indicators of disease trait (risk factor or risk marker) and diagnostic markers (recognizing overt disease, p2335, right column, first paragraph). For diagnostic markers, features such as high sensitivity, specificity, and predictive values are important (p2336, left column and Table 2). However, MCP-1 does not possess one of the important features of diagnostic markers as MCP-1 has been

implicated in the pathogenesis of a variety of diseases that involve monocyte infiltration, including psoriasis, rheumatoid arthritis, and atherosclerosis and elevations of the serum concentration of MCP-1 are associated with inflammation, including alcoholic liver disease, interstitial lung disease, sepsis, and systemic lupus erythematosus. Consequently, MCP-1 lacks specificity as it is associated with variety of diseases other than atherosclerosis and therefore the increased risk of atherosclerosis would not be predicted by determining the presence/amount of MCP-1 alone, which is further supported by Takebayashi et al. (*J. Diabetes and Its Complications*, 2006, Vol. 20, pp98-104). Takebayashi et al. teaches that MCP-1 may not be a marker for atherosclerosis in non-obese Type 2 diabetic patients (see entire document, particularly Abstract). Further, Lindon (*Preclinica*, 2003, Vol. 1, p221) teaches that realization that single markers of complex processes are unlikely to be definitive means that the concept and definition of what constitutes a biomarker has to evolve (see entire document, particularly 2nd paragraph). Taken together, MCP-1 does not satisfy features of indicator (risk marker/factor) for atherosclerosis, as MCP-1 is an indicator of variety of diseases other than atherosclerosis as discussed above and the presence or amount of MCP-1 alone is not capable of specifically assessing the increased risk of atherosclerosis in a human subject.

The current specification (Fig. 2 and p83, paragraph [0254]) shows the association of MCP-1 to subclinical atherosclerosis in 2733 patients who had an EBCT scan. Of these, 581 patients had evidence of subclinical atherosclerosis defined as a coronary calcification score $\geq$ 10. Therefore, the example in the current specification

fails to demonstrate that MCP-1 alone can be used as a specific indicator of atherosclerosis since only 581 patients were confirmed as having an evidence of subclinical atherosclerosis determined using coronary calcification score among 2733 patients, who showed subclinical atherosclerosis as measured by the presence/amount of MCP-1.

The claims are directed to assaying for additional subject-derived specific markers of myocardial injury, neural tissue injury, blood pressure regulation, coagulation, hemostasis, inflammation, and apoptosis and the currently recited claims (40 and 41) would include list of markers disclosed in the current specification (216 markers, pp58-62) as well as those markers not listed in the specification. The specification discloses that MCP-1 and optionally one or more of these additional markers can be used as part of diagnostic panel, which may comprise 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, or more of individual markers, wherein at least one of the individual markers is MCP-1 (pp13-14, paragraph [0039]), which means that there are at least more than $2x10^{216}$ different panels that can be made up from various possible marker combinations, i.e. $2x10^{216}$ different assays measuring different sets of markers in order to carry out the claimed invention. However, the specification fails to provide specific panel of MCP-1 and additional marker combinations, which can be used to identify an increased risk of atherosclerosis in a human subject. Therefore, the specification fails to teach the skilled artisans how to detect all subject-derived markers in all sample types and how to use this information to identify an increased risk of atherosclerosis in a human subject.

The courts have stated that "tossing out the mere germ of an idea does not constitute enabling disclosure." *Genentech*, 108, F.3d at 1366 (quoting *Brenner v. Manson*, 383 U.S. 519, 536 (1996) (stating, in context of the utility requirement, that a "patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion"). "[R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention." Id. The courts have further stated that "if mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses are later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing unproved hypothesis." *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297 (CA FC 2005).

In the instant case, such reasonable detail is lacking. The specification lists a large number of different subject-derived markers, and suggests that one skilled in the art would use information relating to the presence or amount of various different combinations of these markers in order to diagnose atherosclerosis in a subject. However, the specification fails to identify which specific panel of markers should be measured in order to diagnose atherosclerosis in a subject. The specification further fails to disclose what levels of each marker would be indicative of atherosclerosis in a subject.

Although the specification outlines art-recognized methodology that can be used in conducting investigational studies to test and validate biomarkers for various diagnostic purposes, such a general roadmap amounts to an invitation to conduct further research, rather than a specific direction required to enable one of ordinary skill in the art to understand and carry out the invention. Hence, this general outline for how to test and validate different sets of biomarkers for diagnosing atherosclerosis in a subject fails to constitute an enabling disclosure in light of complexity, unpredictability and laborious nature of biomarker validation (discussed further below) and furthermore fails to provide one skilled in the art with any reasonable expectation of success in using any particular combination of markers to identify an increased risk of atherosclerosis in a human subject. The specification sets forth a research plan, not an invention to be practiced.

As a result, in order to carry out the claimed invention, one skilled in the art would first need to determine whether any given set of markers claimed could in fact be used diagnostically, i.e. whether the markers claimed are actually valid biomarkers of the atherosclerosis in a subject, which would mean conducting large-scale clinical investigations in order to compare the levels of each marker in both control and disease patients, and to determine whether statistically significant changes in marker levels are observed and correlated with current gold-standard clinical diagnostic methods. In addition, one skilled in the art would also need to determine what levels or ranges of levels of each of the markers would be indicative of atherosclerosis in a subject. Such investigative research to test and validate all of the biomarkers for use in identifying an

increased risk of atherosclerosis in a subject is not of a routine nature and clearly represents an undue burden.

For example, Bast, Jr. et al. (*Clinical Cancer Research*, 2005, Vol. 11, pp6103-6108) point to the "lengthy process" of assay development and validation and note that many markers that correlate with disease statistically may not prove to be useful clinically (p6105, right column). Similarly, LaBaer et al. (*Journal of Proteome Research*, 2005, Vol. 4, pp1053-1059) teaches that crucial validation steps are needed to demonstrate that an identified biomarker is a reliable predictor and also that the process of converting such a biomarker into a practical clinical test is even more daunting (p1053, paragraph bridging the left and right columns). In addition, Baker (*Nature Biotechnology*, 2005, Vol. 23, pp297-304) speaks to the unpredictability involved in clinically applying biomarkers (p298, *Walking on Thin Ice*).

In summary, the specification fails to teach that MCP-1 alone can be used to identify an increased risk of atherosclerosis in a human subject and the specification lists a large number of possible subject-derived markers and suggests the use of various combinations of the subject-derived markers for identifying an increased risk of atherosclerosis in a human subject. However, the specification lacks clinical data validating the various biomarker combinations corresponding to the atherosclerosis in a human subject, and fails to disclose specific guidance regarding, which specific panels of markers are to be used to identify an increased risk of atherosclerosis in a human subject and what levels would be indicative of an increased risk of atherosclerosis in human a subject. Taken together with the breadth of the claims, lack of examples,

unpredictability associated with validation of biomarkers for clinical use, and current state of the art, which teaches that MCP-1 may be not be a specific marker for atherosclerosis, the specification fails to teach the skilled artisan how to make and use the claimed invention in its full scope without further undue experimentation.

Claim Rejections - 35 USC § 112, Second Paragraph

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 33, 35, and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. In claim 33 and all dependent claims thereof, the term "a concentration of monocyte chemoattractant protein-1" in lines 4-5 and 6-7 is vague and indefinite. It is unclear whether or not the term "a concentration of monocyte chemoattractant protein-1" in lines 4-5 and 6-7 is referring to "the concentration of monocyte chemoattractant protein-1" in lines 2-3. For the purpose of examination, the term "a concentration of monocyte chemoattractant protein-1 or a marker related thereto" in lines 4-5 and 6-7 has been interpreted as referring to "the concentration of monocyte chemoattractant protein-1" in lines 2-3. Applicant is suggested to replace "a" to "the" or said" in the term

"a concentration of monocyte chemoattractant protein-1" in lines 4-5 and 6-7 to obviate this rejection.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. The instant claims recites "method of diagnosing atherosclerosis in a subject (p2, paragraph [0024]), comprising." According to MPEP § 2111.03, "comprising" in a method claim indicates that the claim is open-ended and allows for additional steps. Therefore, the instant claims have been interpreted as including additional steps in order to diagnose or detect presence or absence of atherosclerosis in a subject for the purpose of art rejection(s).

16. Claims 32, 33, 43, and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by Parthasarathy et al. (U.S. PG Pub. No. US 2002/0052000 A1, Filed on Sept. 19, 1997).

Parthasarathy et al. teaches a method of diagnosing atherosclerosis in a subject (p2, paragraph [0024]), comprising:

- determining the presence or amount of MCP-1 in a sample from the subject (p7, paragraphs [0097] and [0098]); and
- correlating the presence or amount of MCP-1 to the presence or absence of atherosclerosis in the subject (p7, paragraphs [0097] and [0098]).

With respect to claim 33, Parthasarathy et al. teaches a method, wherein the correlating step comprises the concentration of MCP-1 to a threshold concentration (statistical norm, p7, paragraphs [0096] and [0097]). The concentration of MCP-1 would inherently be indicative of a first risk of subclinical atherosclerosis if the concentration of MCP-1 were less than the threshold concentration and indicative of a second risk of subclinical atherosclerosis if the concentration of MCP-1 is greater than the threshold concentration.

With respect to claims 42 and 43, Parthasarathy et al. teaches a method of diagnosing atherosclerosis in a subject, wherein the sample is human plasma (p2, paragraph [0024]).

With respect to claim 44, Parthasarathy et al. teaches a method of diagnosing atherosclerosis in a subject, wherein the assay method is an immunoassay method (p7, paragraph [0098]).

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

19. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20. Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Parthasarathy et al. (U.S. PG Pub. No. US 2002/0052000 A1, Filed on Sept. 19, 1997) in view of Adelman et al. (U.S. Patent No. 5,482,935, Jan. 9, 1996).

Parthasarathy et al. teaches a method of diagnosing atherosclerosis in a subject as discussed above. However, Parthasarathy et al. fails to teach a method, wherein the correlating step further comprises determining the presence or amount of risk factor, wherein the risk factor is sex.

Adelman et al. teaches that several risk factor have been identified in individuals who develop atherosclerosis. It can be inferred that persons with at least one risk factor will be at greater risk of developing atherosclerosis than persons with no risk factors. The risk factors include hyperlipidemia, hyperglycemia, diabetes, hypertension, obesity, cigarette smoking, familial hyperlipoproteinemia, aging and male sex.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to further include a method of correlating the presence or amount of risk factor such as hyperlipidemia, hyperglycemia, diabetes, hypertension, obesity, cigarette smoking, familial hyperlipoproteinemia, aging and male sex to the risk of developing atherosclerosis as taught by Adelman et al. in the method of Parthasarathy et al. in order to provide additional sensitivity for the diagnosis of atherosclerosis. The advantage of determining additional information regarding high risk factors for development of atherosclerosis provides the motivation to combine teachings of Parthasarathy et al. and Adelman et al. with a reasonable expectation of success.

21. New Grounds of Rejection

It has been noted that claims 35 and 36 were not properly rejected under art in the previous Office Action dated December 1, 2007. Therefore, the following new ground of rejection has been applied to claims 35 and 36.

Claim 35 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parthasarathy et al. (U.S. PG Pub. No. US 2002/0052000 A1, Filed on Sept. 19, 1997) in view of Duffus et al. (Glossary for chemists of terms used in toxicology, Pure Appl. Chem., 1993, Vol. 65, pp2003-2122).

Parthasarathy et al. teaches a method of identifying an increased risk of atherosclerosis in a human subject as discussed above. However, Parthasarathy et al. fails to teach a method, wherein the threshold concentration provides an odds ratio of about 2 or greater or about 0.5 or less.

Duffus et al. defines odds ratio to be a quotient obtained by dividing one set of odds by another. The risk odds ratio is the ratio of the odds in favor of getting disease and disease odds ratio is a quotient obtained by dividing diseased set of odds by the non-diseased set (threshold concentration, p2078).

Kieback teaches a method of using odds ratio provided by for indicating an increased risk for a disease (breast or ovarian cancer, see entire document).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to employ the odds ratio obtained from a threshold concentration of Duffus et al. in the method of Parthasarathy et al. in order to quantitatively assess the

risk of developing atherosclerosis in a human subject. The advantage of using a quantitative analysis for assessing risk of a disease such as atherosclerosis provides the motivation to combine teachings of Parthasarathy et al. and Duffus et al.. Further, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in employing the odds ratio of Duffus et al. in the method of Parthasarathy et al. since the use of odds ratio in assessing risk for a disease based on results of subject-derived markers is well known as taught by Kieback.

With respect to the limitations of specific range of odds ratios (odds ratio of about 1.3 or greater or about 0.77 or less and odds ratio of about 2 or greater or about 0.5 or less), it has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value for a result effective variable. Section 2144.05 [R3] of the MPEP presents case law upholding obviousness rejections based on optimization of ranges:

A. Optimization Within Prior Art Conditions or Through Routine Experimentation

> Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed

> elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.)

However, the specification does not disclose that the specifically claimed range(s) of "odds ratio of about 1.3 or greater or about 0.77 or less and odds ratio of about 2 or greater or about 0.5 or less" is for any particular purpose or to solve any stated problem that distinguishes it from the other ranges disclosed. The specification therefore lacks disclosure of the criticality required by the Courts in providing patentability to the claimed range(s).

In addition to a lack of disclosed criticality in the specification, an obviousness rejection based upon optimization must rely on prior art that discloses the optimized parameter is a result-effective variable. See MPEP 2144.05:

B. Only Result-Effective Variables Can Be Optimized

> A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio, and therefore the parameter optimized was not recognized in the art to be a result-effective variable.). See also *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) (prior art suggested proportional balancing to achieve desired results in the formation of an alloy).

Since Parthasarathy et al. in view of Duffus et al. and Kieback teach that odds ratios provided by a threshold concentration can be assessed for a subject-derived markers, the prior art therefore provides teaching that the odds ratio is a variable that

achieves a recognized result, and satisfies the above requirement of a result-effective variable in order to set forth an obviousness rejection based on optimization.

Because Applicants fail to disclose that the claimed range(s) of "odds ratio of about 1.3 or greater or about 0.77 or less and odds ratio of about 2 or greater or about 0.5 or less" provides a criticality to the invention that separates it from the other ranges in the specification, and the prior art discloses that odds ratios provided by a threshold concentration can be assessed for a subject-derived markers, it would therefore have been obvious for one of ordinary skill to discover the optimum workable range(s) of "odds ratio of about 1.3 or greater or about 0.77 or less and odds ratio of about 2 or greater or about 0.5 or less" by normal optimization procedures known in the clinical chemistry arts.

22. Claim 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parthasarathy et al. (U.S. PG Pub. No. US 2002/0052000 A1, Filed on Sept. 19, 1997) in view of Carville et al. (*Clinical Chemistry*, 1996, Vol. 42, pp1537-1541).

Parthasarathy et al. teaches a method of diagnosing atherosclerosis in a subject as discussed above. However, Parthasarathy et al. fails to teach a method, further comprising determining the presence or amount of specific markers of myocardial injury.

Carville et al. teaches that acute myocardial injury (AMI) occurs by occlusive thrombosis after rupture of atherosclerotic lesions in the coronary arteries (p1537, *Introduction*, 3rd paragraph) and AMI is associated with release of cardiac muscle cell proteins including creatine kinase (CK) and its MB isoenzyme (CKMB), troponin and

myoglobin (pp1537-1538, *Introduction*, 4th paragraph). Detection of these necrotic markers form the basis of diagnostic tests for MI (pp1537-1538, *Introduction*, 4th paragraph). Further, thrombus precursor protein (TpP™) has a potential to be a beneficial aid in patient selection for early detection MI and permit more timely therapeutic intervention (pp1537-1538, *Introduction*, 4th paragraph) as TpP™ is an earlier marker of thromobosis compared to necrotic markers (CK, CKMB, troponin, and myoglobin).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to further include determining the presence or amount of specific markers of myocardial injury as taught by Carville et al. in the method of Parthasarathy et al. in order to determine risk of rupture of atherosclerotic lesions. The advantage of providing early diagnosis of atherosclerotic lesion rupture provides the motivation to combine teachings of Parthasarathy et al. and Carville et al. with a reasonable expectation of success as the early diagnosis of atherosclerotic lesion rupture has a potential to be a beneficial aid in patient selection for early detection MI and permit more timely therapeutic intervention.

Response to Arguments

23. Rejection of claims 32-44 under 35 U.S.C. 112, first paragraph (written description)

Regarding claims 32-36, 43, and 44, Applicant's arguments, see pp8-12, filed on April 2, 2007, the rejection of claims 32-39, 43, and 44 under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement have been

withdrawn in view of amended claim 32 and canceled claims 39-39 and 42 in the reply filed on April 2, 2007.

Regarding claims 40 and 41, Applicant's arguments filed on April 2, 2007 have been fully considered but they are not persuasive in view of the previously stated grounds of rejection (Office Action dated December 1, 2006, item 10). As stated above (see item 9), the MPEP does state that for a generic claim, the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. In the instant case, the claims are not limited as to the number of markers, since claims 40 and 41 recite "determining the presence or amount of one or more subject-derived markers" and would encompass, for example 216 different subject-derived markers as disclosed in the current specification (pp58-62) as well as those markers not listed in the specification. Further, claim 41 is directed to assaying for additional subject-derived specific markers of myocardial injury, neural tissue injury, blood pressure regulation, coagulation, hemostasis, inflammation, and apoptosis and the currently recited claims would include list of markers disclosed in the current specification (216 markers, pp58-62) as well as those specific markers not listed in the specification. It does not appear based upon the limited disclosure of additional subject-derived specific markers of myocardial injury, neural tissue injury, blood pressure regulation, coagulation, hemostasis, inflammation, and apoptosis alone that Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the limited number of species disclosed and the extensive variation permitted within the genus "subject-

derived specific markers of myocardial injury, neural tissue injury, blood pressure regulation, coagulation, hemostasis, inflammation, and apoptosis."

24. Rejection of claims 32-36, 40, 41, 43, and 44 under 35 U.S.C. 112, first paragraph (enablement)

Applicant's arguments filed on April 2, 2007 have been fully considered but they are not persuasive in view of previously stated grounds of rejection (Office Action dated December 1, 2006, item 11).

Applicant's argument (pp13-15) that interpretation of publications (Vasan, Bast, Jr. et al., LaBaer et al., Baker, and Takebayashi et al.) used in the Office Action dated December 1, 2006 (item 11) do not accurately represent the teachings of these publication is not found persuasive as the above publications clearly teaches that characteristics of high sensitivity, specificity, and predictive values are important factors for biomarkers for diagnostic and prognostic (risk of subclinical assessment). Although the usage of biomarkers are common in the diagnostic and prognostic assays, biomarker such as MCP-1, which is well known in the art to be present in variety of disease conditions as disclosed in the current specification (p23), would not be capable of identifying an increased risk of atherosclerosis since the assay result of MCP-1 may indicate presence of absence of disease conditions other than atherosclerosis. Further, Lindon (*Preclinica*, 2003, Vol. 1, p221) teaches that realization that single markers of complex processes are unlikely to be definitive means that the concept and definition of what constitutes a biomarker has to evolve (see entire document, particularly 2nd

paragraph). As MCP-1 is not a specific marker of atherosclerosis, a panel of markers rather than a single marker would be necessary for assessing a risk of atherosclerosis.

Applicant's argument that the skill in the art is extremely high and would be prepared to perform the necessary studies to practice the claimed method is not found persuasive in view of previously stated grounds of rejection. As stated previously (item 11 of Office Action dated December 1, 2007), Bast, Jr. et al. points to the "lengthy process" of assay development and validation and note that many markers that correlate with disease statistically may not prove to be useful clinically, LaBaer et al. teaches that validation steps are crucial to demonstrate that an identified biomarker is a reliable predictor, and Baker discusses to the unpredictability involved in clinically applying biomarkers. Takebayashi et al. further supports the unpredictability involved in clinically application of MCP-1, as Takebayashi et al. teaches that MCP-1 may not be a marker for atherosclerosis in non-obese Type 2 diabetic patients. Since the clinical application of biomarkers requires "lengthy process" of clinical validation, which is unpredictable, the specification fails to teach a skilled artisan how to make and use the claimed invention in its full scope without further undue experimentation. Based on the teachings of the above-mentioned references, Applicant's argument regarding predictability of the art (pp16 and17) is not found persuasive.

The argument regarding the quantity of experimentation necessary (p16) is not found persuasive, as the courts have stated, "tossing out the mere germ of an idea does not constitute enabling disclosure."

The arguments regarding the amount of direction or guidance and the working examples (p17) is not found persuasive as the working example of the current specification only provides data for association of MCP-1 to subclinical atherosclerosis in 2733 patients. Of these 2733 patients, only 581 patients (22%) had evidence of subclinical atherosclerosis defined as a coronary calcification score ≥ 10. Therefore, the example in the current specification fails to demonstrate that MCP-1 alone can be used as a specific prognostic marker (risk indicator) of atherosclerosis since only 22% of the patients showing subclinical atherosclerosis as measured by the presence/amount of MCP-1 were confirmed as having an evidence of subclinical atherosclerosis determined using coronary calcification score. As MCP-1 has been associated with other disease conditions such as inflammation and cardiovascular diseases, the presence/amount of MCP-1 in remaining 2152 patients (showing subclinical atherosclerosis as measured by the presence/amount of MCP-1) may in fact be due to disease conditions other than atherosclerosis.

The argument regarding breath of claims (p18) is not found persuasive in view of previously stated grounds of rejection. The claims are not limited as to the number of markers, since claims 40 and 41 recite "determining the presence or amount of one or more subject-derived markers" and would encompass, for example 216 different subject-derived markers as disclosed in the current specification (pp58-62) as well as those markers not listed in the specification. Further, claim 41 is directed to assaying for additional subject-derived specific markers of myocardial injury, neural tissue injury, blood pressure regulation, coagulation, hemostasis, inflammation, and apoptosis and

the currently recited claims would include list of markers disclosed in the current specification (216 markers, pp58-62) as well as those specific markers not listed in the specification. However, the specification fails to provide specific panel of MCP-1 and additional marker combinations, which can be used to identify an increased risk of atherosclerosis in a human subject. Therefore, the specification fails to teach the skilled artisans how to detect all subject-derived markers and how to use this information to identify an increased risk of atherosclerosis in a subject.

25. Rejection of claims 32, 33, 43, and 44 under 35 U.S.C. 102(b) as being anticipated by Parthasarathy et al.

Applicant's arguments filed on April 2, 2007 have been fully considered but they are not persuasive in view of previously stated grounds of rejection (see Office Action dated December 1, 2006, item 27).

It has been noted that claim 33 have been inadvertently excluded from the rejection under 35 U.S.C. 102(b) as being anticipated by Parthasarathy et al. Claim 33 has now been included in the rejection under 35 U.S.C. 102(b) as being anticipated by Parthasarathy et al. as set forth above (see item # above).

Applicant's argument that Parthasarathy et al. does not indicate that MCP-1 can be used to identify an increased risk of subclinical atherosclerosis is not found persuasive, as the method of Parthasarathy et al. teaches a prognostic method for atherosclerosis (p7, paragraph [0097]), which would read on a method of identifying an increased risk of subclinical atherosclerosis. The method of Parthasarathy et al. involves detection of variety of markers including HDH, LDL, and triacylglyceride and

surrogate markers, which include MCP-1. Therefore, the method of Parthasarathy et al. anticipates the claimed invention as the instant claims recites a translational phrase "comprising," which does not exclude other methods steps (i.e. detection of markers including HDH, LDL, and triacylglyceride).

26. Rejection of claim 34 under 35 U.S.C. 103(a) as being unpatentable over Parthasarathy et al. in view of Adelman et al.

Applicant's arguments filed on April 2, 2007 have been fully considered but they are not persuasive in view of previously stated grounds of rejection (see Office Action dated December 1, 2006, item 31).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the advantage of determining additional information regarding high risk factors for development of atherosclerosis provides the motivation to combine teachings of Parthasarathy et al. and Adelman et al. with a reasonable expectation of success. Further, it has long been held that it is obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose. *In re Kerkhoven*, 626, F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

27. Rejection of claims 40 and 41 under 35 U.S.C. 103(a) as being unpatentable over Parthasarathy et al. in view of Carville et al.

Applicant's arguments filed on April 2, 2007 have been fully considered but they are not persuasive in view of previously stated grounds of rejection (see Office Action dated December 1, 2006, item 32).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the advantage of providing early diagnosis of atherosclerotic lesion rupture provides the motivation to combine teachings of Parthasarathy et al. and Carville et al. with a reasonable expectation of success as the early diagnosis of atherosclerotic lesion rupture has a potential to be a beneficial aid in patient selection for early detection MI and permit more timely therapeutic intervention. Further, it has long been held that it is obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose. *In re Kerkhoven*, 626, F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

28. Since the prior art fulfills all the limitations currently recited in the claims, the invention as currently recited would read upon the prior art.

Conclusion

29. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Harrington (*Stem Cells*, 2000, Vol. 18, pp65-66) teaches a role of MCP-1 in pathogenesis of atherosclerosis (see entire document).

30. No claim is allowed.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Unsu Jung whose telephone number is 571-272-8506. The examiner can normally be reached on M-F: 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Unsu Jung, Ph.D.
Patent Examiner
Art Unit 1641

LONG V. LE 07/08/07
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600